D2

PATENT SPECIFICATION

(11) **1 300 419**

1300419

NO DRAWINGS

(21) Application No. 25025/69 (22) Filed 16 May 1969
(21) Application No. 18467/70 (22) Filed 17 April 1970
(23) Complete Specification filed 6 May 1970
(45) Complete Specification published 20 Dec. 1972
(51) International Classification C07D 43/28 // A61K 27/00
(52) Index at acceptance
C2C 174—175—185 183—193—277 184—190—275 200 214 225 226 22Y 255 25Y 29X 29Y 30Y 351 352 364 366 368 36Y 389 491 624 625 628 658 672 67X 760 790 79Y TY

(72) Inventors WILLIAM ROGER BUCKETT and HANS HAROLD BOSMAN

(54) NEW MORPHINONE DERIVATIVES AND THEIR PREPARATION

(71) We, ORGANON LABORATORIES LIMITED, a British Company, of Crown House, London Road, Morden, Surrey, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

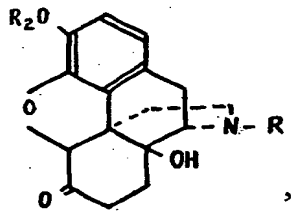
This invention relates to novel morphinone derivatives and more particularly to esters of 14 - hydroxy - dihydronormorphinone derivatives.

Chemically, the morphinone derivatives belong to the morphine and morphine-like substances. Morphine, which is a strong analgetic, has the disadvantage of readily inducing harmful morphine addiction. Nalorphine, an N-allyl derivative of morphine, is known to have reasonable analgetic properties and to be a good morphine antagonist, but it has the undesirable side effect of inducing hallucinogenic phenomena. Generally, the biological activities of the morphine-like substances are widely different.

An important step in the field of analgetic substances was the discovery of N-substituted 14-hydroxy-dihydronorcodeinone derivatives as reported in Belgian Patent No. 691,715. This Belgian patent describes 14 - hydroxy - dihydronorcodeinone derivatives which one substituted at the nitrogen atom with a dimethylallyl, cyclopropyl - methyl- or cyclobutylmethyl radical. These derivatives show good analgetic properties without however inducing the known side effects accompanying the use of morphine.

The present invention constitutes a further step forward in that we have now found a class of novel 3 - alkoxy - 14 - hydroxy - N - substituted - dihydronormorphinone derivatives with surprisingly improved analgetic properties, especially in oral administration, and with a much better combination of other activities in comparison with all known analgetic substances.

Accordingly, the invention is directed to a method for the preparation of novel 3 - alkoxy-N - substituted - 14 - acyloxy - dihydronormorphinone and acid addition salts thereof in which a compound of the general formula:



, in which

R is an allyl, dimethylallyl, cyclopropylmethyl or cyclobutylmethyl radical, and

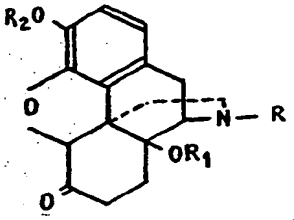
R_2 is an alkyl group having 1—6 carbon atoms, is esterified with an aliphatic, cycloaliphatic, araliphatic aromatic or heterocyclic carboxylic acid with 1—18 carbon atoms, after which, if desired, the compound obtained is converted into an acid addition salt.

A preferred starting material is a compound of the above formula in which R is a cyclopropylmethyl group. Preferably, aliphatic carboxylic acids with 2—10 carbon atoms are used for the esterification.

The invention also extends to novel compounds which are esters of N - substituted - 14 - hydroxy - dihydronormorphinone deri-

[*Price 25p*]

vatives having the general formula:



R is an allyl, dimethylallyl, cyclopropylmethyl or cyclobutyl-methyl group,

R_1 is an aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic acyl group derived from an aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic carboxylic acid with 1—18 carbon atoms, and

R_2 is a alkyl group with 1—16 carbon atoms, as well as the acid addition salts thereof.

The noval compounds show very useful properties in that they have good analgetic, tranquillizing, cough-suppressing and anti-convulsant properties, especially in oral administration. The compounds do not induce or support drug dependence. They are extremely valuable in post-operative treatment of patients because of their analgetic, psychosedative, anti-convulsant and lack of respiratory depressant properties.

The most favourable properties are found in the series of aliphatic esters with 2—10 carbon atoms and, more particularly, in the lower (C: 2—10) aliphatic esters of 3-alkoxy-14 - hydroxy - N - cyclopropylmethyl - dihydronormorphinone and of 3 - alkoxy - 14-hydroxy - N - dimethylallyl - dihydronormorphinone.

Examples of suitable compounds according to the invention are: N - dimethylallyl - 14 - acetoxy - dihydronorcodeinone, N - cyclopropylmethyl - 14 - acetoxy - dihydronorcodeinone, N - cyclobutylmethyl - 14 - acetoxy-dihydronorcodeinone, N - dimethylallyl - 14 - propionyloxy - dihydronorcodeinone, N - cyclopropylmethyl - 14 - caproyloxy - dihydronorcodeinone, N - cyclopropylmethyl - 14 - valeryloxy - dihydronorcodeinone, N - cyclobutylmethyl - 14 - propionyloxy - dihydronorcodeinone, N - allyl - 14 - caproyloxy - dihydronorcodeinone and the corresponding compounds with higher ester groups at the 14-position. Other examples of suitable compounds are those in which the methoxy group in the 3-position is replaced by an ethoxy group such as, for example, N-dimethylallyl-3 - ethoxy - 14 - acetoxy - dihydronormorphinone and the corresponding HCl and HBr salts. From a pharmacological viewpoint, the following compounds are preferred: N - dimethylallyl - 14 - propionyloxy - dihydronorcodeinone, N - cyclopropylmethyl - 14 - caproyloxy - dihydronorcodeinone and N - cyclopropylmethyl - 14 - valeryloxy - dihydronorcodeinone.

As already indicated, the novel compounds according to this invention are prepared by esterification of a 3 - alkoxy - N - substituted-14 - hydroxy - dihydronormorphinone with an aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic carboxylic acid having 1 to 18 carbon atoms. The 3 - alkoxy - N - substituted - 14 - hydroxy - dihydronormorphinone used as a starting material can be obtained in various ways. For example 14 - hydroxy - dihydrocodeinone can be acylated in the 14 - position, e.g. with acetic acid anhydride, the N - methyl group in the resculting product being then replaced by an N - cyano group by reaction with bromocyan, whereupon the cyano group is removed with a strong acid e.g. sulphuric acid, thus yielding 14 - hydroxy - dihydronorcodeinone. This latter compound is a suitable starting material to obtain the various N - substituted - 14 - hydroxy - dihydronorcodeinones. Thus, it can be reacted with dimethylallylbromide to yield N - dimethylallyl - 14 - hydroxy - dihydronorcodeinone. The corresponding N - substituted derivatives can be obtained by means of reaction with cyclopropylmethylbromide or cyclobutylmethylbromide. An alternative method comprises the conversion of 14 - hydroxy - dihydronorcodeinone with glycol into the corresponding ethyleneketal, which is converted in turn by reaction with cyclopropylcarbochloride or cyclobutylcarbochloride into the corresponding N - cyclopropylcarboxyl or N - cyclobutylcarboxyl compound. The subsquent reduction of the latter compound with lithium aluminium hydride, followed by the splitting-off of the ethyleneketal group by boiling with acid, yields the corresponding N - cyclopropylmethyl- or N - cyclobutylmethyl - 14 - hydroxy - dihydronorcodeinone.

The acid addition salts of compounds falling within the above general formula are also within the scope of the present invention. Generally speaking, such salts are preferred due to their better physical properties. By "acid addition salts" are meant the salts derived from therapeutically-acceptable organic or inorganic acids such as HCl, HBr, phosphoric acid, maleinic acid, fumaric acid, succinic acid, citric acid, acetic acid, glutamic acid and aspartic acid.

The following pharmacalogical data demonstrate the superiority of the compounds according to the invention in comparison with 14 - hydroxy - N - substituted - dihydronorcodeinone.

Analgetic properties:

Writhing test:

Intraperitonial injection of phenyl - p - benzoquinone in mice elicits a characteristic writhing syndrome. Premedication by oral administration or subcutaneous injection with drugs abolishes or reduces the syndrome. The method consists in comparing the number of

writhing movements in drug-treated animals with the mean of control groups. The figures given in Table I demonstrate the "ED 50 values", which means the dose of drugs to produce 50% reduction of the writhing movements within a given time.

TABLE I

Substance*	Analgetic writhing test	
	subc. ED 50 in mg/kg body weight	*oral* ED 50 in mg/kg body weight
Reference compounds:		
14-hydroxy-N-cyclopropylmethyl-dihydronorcodeinone	31,5	>100
14-hydroxy-N-dimethylallyl-dihydronorcodeinone	12,5	inactive
14-hydroxy-N-cyclobutylmethyl-dihydronorcodeinone	2,7	inactive
14-hydroxy-N-allyl-dihydronorcodeinone	7,8	,<100
Novel compounds:		
14-acetoxy-N-cyclopropylmethyl-dihydronorcodeinone	4,3	1—10
14-butyryloxy-N-cyclopropylmethyl-dihydronorcodeinone	3,4	48,8
14-valeryloxy-N-cyclopropylmethyl-dihydronorcodeinone	0,25	5,19
14-caproyloxy-N-cyclopropylmethyl-dihydronorcodeinone	0,32	5,25
14 - oenanthyloxy - N - cyclopropylmethyl-dihydronorcodeinone	1,2	23,5
14-oenanthyloxy-N-dimethylallyl-dihydronorcodeinone	24	60,7
14-valeryloxy-N-cyclobutylmethyl-dihydronorcodeinone	0,5	5,8
14-caproyloxy-N-allyl-dihydronorcodeinone	4,4	10

*each substance was tested as a free base or salt.

From Table I, it will be seen that, especially in oral administration, the analgetic properties of the compounds according to the invention are remarkably improved in comparison with the properties of the reference compounds.

Acute toxicity:

The acute toxicity of the compounds was determined in albino male mice using subcutaneous, intravenous and oral routes of administration. Groups of ten mice were used and observed for effects at 24 hours and 5 days. The 50% lethal dose (LD 50 value) is based on the latter time interval. The results obtained are set out in Table II.

TABLE II

Substance*	LD 50 value in mg/kg body weight		
	intravenous	*subcutaneous*	*oral*
Reference compounds			
14 - hydroxy-N-allyl-dihydronorcodeinone	105	>300	>300
14-hydroxy-N-dimethylallyl-dihydronorcodeinone	89	>300	>300
14-hydroxy-N-cyclopropylmethyl-dihydronorcodeinone	67	>300	>300
Novel compounds:			
14-propionyloxy-N-allyl-dihydronorcodeinone	192	>300	>300
14-caproyloxy-N-allyl-dihydronorcodeinone	258	>300	>300
14-caproyloxy-N-dimethylallyl-dihydronorcodeinone	465	>300	>300
14-propionyloxy-N-dimethylallyl-dihydronorcodeinone	112	>300	>300
14-propionyloxy-N-cyclopropylmethyl-dihydronorcodeinone	92	>300	>300
14-acetoxy-N-cyclopropylmethyl-dihydronorcodeinone	105	>300	>300
14-caproyloxy-N-cyclopropylmethyl-dihydronorcodeinone	165		

*each substance was tested as a free base or salt.

From Table II, it will be seen that the acute toxicity of the compounds according to the invention is of the same order as that of the reference compounds in oral or subcutaneous administration, but improved in intravenous administration.

The compounds according to the invention exert further an improved action on the central nervous system, e.g. an improved psychosedative effect, in comparison with known drugs. They do not induce or support drug dependence and do not depress respiration.

The compounds can be administered orally or parenterally, preferably in doses of 20—50 mg per day. For oral administration, the compounds can be compressed into tablets, preferably mixed with excipients, or they can be administered in the form of a powder in capsules. For injection purposes, the compounds are brought into solutions, suspensions or emulsions.

The following examples illustrate the method of preparation of the above componds.

Example I

6.4 g of N - dimethylallyl - 14 - hydroxy - dihydronorcodeinone were dissolved in 30 ml of benzene. 14 ml of acetic acid anhydride were added to the solution, whereupon the mixture was boiled with reflux for 1 1/2 hours. The benzene was distilled off and the residue was poured into water. The pH of the mixture was adjusted to 9 with a sodium carbonate solution and was subsequently extracted with benzene (four times).

The combined benzene extracts were concentrated to dryness and the residue was dissolved in ethanol. Acidification of the ethanolic solution with concentrated hydrochloric acid yielded 5.3 g of N - dimethylallyl - 14 - acetoxy - dihydronorcodeinone - HCl (melting point 145.0—146.5°C).

Example II

In a similar manner to the method of Example I there were prepared:
N - cyclopropylmethyl - 14 - acetoxy - dihydronorcodeinone.HCl; melting point: 250—251.5°C,
N - allyl - 14 - acetoxy - dihydronorcodeinone.HCl; melting point: 258—258.5°C, and
N - cyclobutylmethyl - 14 - acetoxy - dihydronorcodeinone; melting point: 188.5—190°C.

Example III

4.1 g of N - dimethylallyl - 14 - hydroxy - dihydronorcodeinone were dissolved in 30 ml of benzene. 5.9 g of propionic acid anhydride were added and the mixture was boiled with reflux for 20 hours. The benzene was distilled

off and the residue was poured into water. The pH of the mixture was adjusted to 9 with a sodium carbonate solution and then extracted with benzene (4 times).

The combined benzene extracts were concentrated. The residue was crystallized from an acetone-water mixture (ratio 4:1) yielding 3.2 g of N - dimethylallyl - 14 - propionyloxy - dihydronorcodeinone (melting point 131.4—132.2°C). The corresponding N-cyclopropylmethyl - derivative was obtained in the same way.

Example IV

30 g of N - cyclopropylmethyl - 14 - hydroxy - dihydronorcodeinone were dissolved 250 ml of toluene. 20 g of butyric acid anhydride were added to the solution and the mixture was boiled with reflux for 11 hours. The toluene was distilled off and the residue was poured into water. The mixture was adjusted to pH 9 with a sodium carbonate solution and then extracted with benzene (5 times). The combined benzene extracts were concentrated to dryness. Crystallization of the residue from an acetone-water (4:1) mixture yielded 18 g of crude ester. Recrystallization from the same solvent (fresh) yielded N - cyclopropylmethyl - 14 - butyryloxy - dihydronorcodeinone (m.p. 84.2—85.4°C).

In the same manner, the 14 - lauroyloxy - derivative was obtained.

Example V

25 g of N - dimethylallyl - 14 - hydroxy-dihydronorcodeinone were dissolved in 250 ml of benzene. 31 g of butyric acid anhydride were added and the mixture was boiled with reflux for 41 hours. The benzene was distilled off and the residue was poured into water. The pH of the mixture was adjusted to 9 with a sodium carbonate solution and extracted with benzene (4 times).

The combined benzene extracts were concentrated to dryness and the residue was dissolved in 150 ml of 3 N acetic acid. The acetic acid solution was adjusted to pH 2 with sulphuric acid and was then extracted with ether. On neutralization of the aqueous phase with a sodium carbonate solution, 24 g of a brownish yellow precipitate were obtained which, on recrystallization from an acetone-water (4:1) mixture, yielded 17 g of N - dimethylallyl - 14 - butyroxy - dihydronorcodeinone (m.p. 82.0—83.5°C).

Example VI

30 g of N-cyclopropylmethyl14-hydroxy-dihydronorcodeinone were converted into N-cyclopropylmethyl - 14 - valeryloxy - dihydronorcodeinone in the same way as described in Example V but using valeric acid anhydride instead of butyric acid an hydride yielding 19 g with melting point 95.5—96.5°C. Similarly, N - dimethylallyl - 14 - hydroxy - dihydronorcodeinone yielded N - dimethylallyl - 14-valeryloxy - dihydronorcodeinone with melting point 102.4—103.6°C, and N - cyclobutylmethyl - 14 - hydroxy - dihydronorcodeinone yielded N - cyclobutylmethyl - 14 - valeryloxy - dihydronorcodeinone with melting point 102—103°C.

Example VII

59 g of N - dimethylallyl - 14 - hydroxy-dihydronorcodeinone were reacted with 51 g of caproic acid anhydride in the same way as described in Example III, except that the residue of the benzene extracts was dissolved in ethanol. To this ethanolic solution, ether was added until turbidity just occurred. On standing in a refrigerator, 33 g of N - dimethylallyl - 14 - caproyloxy - dihydronorcodeinone were obtained as crystals (m.p. 85.4—86.5°C).

In the same way, N - cyclopropylmethyl - 14 - caproyloxy - dihydronorcodeinone (m.p. 102—104°C) and N - cyclobutylmethyl - 14-caproyloxy - dihydronorcodeinone (m.p. 108—109°C) were obtained.

Example VIII

49 g of N - cyclopropylmethyl - 14-hydroxy - dihydronorcodeinone were added to 140 cc. heptanoic acid anhydride. The solution was heated to 110°C with stirring and kept at that temperature for 2 hours. The mixture was cooled and poured into water, whereupon the pH was adjusted to 9 with a solution of sodium carbonate. The mixture was then extracted with benzene (4 times). The combined benzene extracts were concentrated to dryness. The residue was dissolved in ether and subjected to chromatography over neutral Al_2O_3. The eluates containing ester were evaporated to dryness. Crystallization of the residue from petroleum ether yields 47 g of N - cyclopropylmethyl - 14 - heptanoyloxy - dihydronorcodeinone (m.p. 87.4—88.2°C). In a similar way, but with recrystallization from an ethanol-water (4:1) mixture, 32 g of N - dimethylallyl - 14 - heptanoyloxy - dihydronorcodeinone (m.p. 66.0—67.2°C) were obtained from 40 g of N - dimethylallyl - 14 - hydroxy - dihydronorcodeinone.

Example IX

In the same way as described above there were prepared:

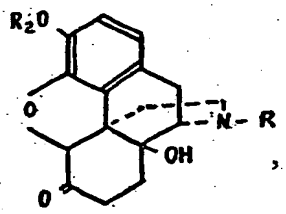
N - allyl - 14 - cinnamoyloxy - dihydronorcodeinone (m.p. 175.6—176.5°C), N - dimethylallyl - 14 - cinnamoyloxy - dihydronorcodeinone (m.p. 125.8—127.2°C) and N - cyclopropylmethyl - 14 - cinnamoyloxy - dihydronorcodeinone (m.p. 149.8—151°C).

Example X

In the same way as described above the following compounds were prepared:
N - allyl - 14 - propionyloxy - dihydronorcodeinone. HCl; m.p. 240—241.5°C (dec.), and N - allyl - 14 - caproyloxy - dihydronorcodeinone.HCl; m.p. 118—119.5°C.

WHAT WE CLAIM IS:—

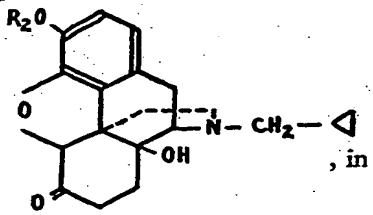
1. A method for the preparation of novel 3-alkoxy - N - substituted - 14 - acyloxy - dihydronormorphinone and acid addition salts thereof in which a compound of the general formula:



, in which

R is an allyl, dimethylallyl, cyclopropylmethyl or cyclobutylmethyl radical, and
R_2 is a alkyl group, having 1—6 carbon atoms is esterified with an aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic carboxylic acid with 1—18 carbon atoms, after which, if desired, the compound obtained is converted into an acid addition salt.

2. A method according to claim 1, in which a compound of the general formula:



, in which

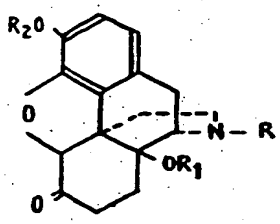
R_2 has the meaning above indicated, is used as the starting material.

3. A method according to claim 1 or claim 2, in which aliphatic carboxylic acids with 2—10 carbon atoms are used for the esterification.

4. A method according to claim 1, in which N - dimethylallyl - 14 - propionyloxy - dihydronorcodeinone or an acid addition salt thereof is prepared.

5. A method according to claim 2, in which N - cyclopropylmethyl - 14 - valeryloxy -or 14 - caproyloxy - dihydronorcodeinone or acid addition salts thereof are prepared.

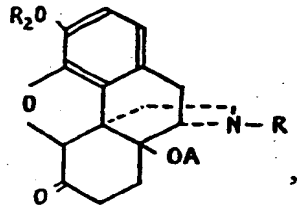
6. Novel compounds of the general formula:



, in which

R is an allyl, dimethylallyl, cyclopropylmethyl or cyclobutylmethyl group,
R_1 is an aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic acyl radical derived from an aliphatic, cycloaliphatic, araliphatic, aromatic or heterocyclic carboxylic acid with 1—18 carbon atoms, and
R_2 is a alkyl group with 1—6 carbon atoms, and the acid addition salts thereof.

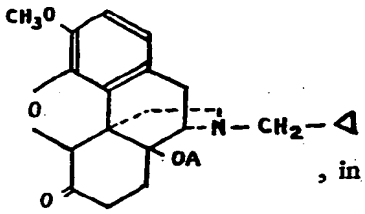
7. Novel compounds of the general formula:



, in which

R and R_2 have the meanings indicated in claim 6 and A is an aliphatic acyl radical derived from an aliphatic carboxylic acid with 2—10 carbon atoms, and the acid addition salts thereof.

8. Novel compounds of the general formula:



, in which

A has the meaning indicated in claim 7, and the acid addition salts thereof.

9. N - cyclopropylmethyl - 14 - valeryloxy - dihydronorcodeinone and acid addition salts thereof.

10. N - cyclopropylmethyl - 14 - caproyloxy - dihydronorcodeinone and acid addition salts thereof.

11. N - dimethylallyl - 14 - propionyloxy - dihydronorcodeinone and acid addition salts thereof.

12. Compounds according to claim 6, wherever prepared by a method according to claim 1.

13. Compounds according to claim 7, whenever prepared by a method according to claim 2.

14. A method according to claim 1 substantially as described in any of the Examples.

15. Compounds according to claim 6 substantially as described in any of the Examples.

BROMHEAD & CO.,
Chartered Patent Agents,
Clifford's Inn,
Fetter Lane,
London, E.C.4.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.